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Axillary Pathologic Complete Response After Neoadjuvant Systemic Therapy by Breast Cancer Subtype in Patients With Initially Clinically Node-Positive Disease

A Systematic Review and Meta-analysis

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IMPORTANCE An overview of rates of axillary pathologic complete response (pCR) for all breast cancer subtypes, both for patients with and without pathologically proven clinically node-positive disease, is lacking.

OBJECTIVE To provide pooled data of all studies in the neoadjuvant setting on axillary pCR rates for different breast cancer subtypes in patients with initially clinically node-positive disease.

DATA SOURCES The electronic databases Embase and PubMed were used to conduct a systematic literature search on July 16, 2020. The references of the included studies were manually checked to identify other eligible studies.

STUDY SELECTION Studies in the neoadjuvant therapy setting were identified regarding axillary pCR for different breast cancer subtypes in patients with initially clinically node-positive disease (ie, defined as node-positive before the initiation of neoadjuvant systemic therapy).

DATA EXTRACTION AND SYNTHESIS Two reviewers independently selected eligible studies according to the inclusion criteria and extracted all data. All discrepant results were resolved during a consensus meeting. To identify the different subtypes, the subtype definitions as reported by the included articles were used. The random-effects model was used to calculate the overall pooled estimate of axillary pCR for each breast cancer subtype.

MAIN OUTCOMES AND MEASURES The main outcome of this study was the rate of axillary pCR and residual axillary lymph node disease after neoadjuvant systemic therapy for different breast cancer subtypes, differentiating studies with and without patients with pathologically proven clinically node-positive disease.

RESULTS This pooled analysis included 33 unique studies with 57 531 unique patients and showed the following axillary pCR rates for each of the 7 reported subtypes in decreasing order: 60% for hormone receptor (HR)–negative/*ERBB2* (formerly *HER2*)–positive, 59% for *ERBB2*-positive (HR-negative or HR-positive), 48% for triple-negative, 45% for HR-positive/*ERBB2*-positive, 35% for luminal B, 18% for HR-positive/*ERBB2*-negative, and 13% for luminal A breast cancer. No major differences were found in the axillary pCR rates per subtype by analyzing separately the studies of patients with and without pathologically proven clinically node-positive disease before neoadjuvant systemic therapy.

CONCLUSIONS AND RELEVANCE The HR-negative/*ERBB2*-positive subtype was associated with the highest axillary pCR rate. These data may help estimate axillary treatment response in the neoadjuvant setting and thus select patients for more or less invasive axillary procedures.

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Supplemental content

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Neoadjuvant systemic therapy (NST) is often considered in patients with axillary lymph node involvement at diagnosis (cN-positive disease). Neoadjuvant systemic therapy may result in complete eradication of invasive cancer in the breast and axillary lymph nodes, defined as pathologic complete response (pCR), which is associated with improved survival compared with residual disease after NST.[1-3] Previous studies[4-6] have reported that axillary pCR has a greater effect on disease-free and overall survival than pCR of the primary breast tumor.

Axillary pCR not only provides prognostic information but may also lead to the omission of conventional axillary lymph node dissection (ALND). Different less invasive axillary staging procedures have been introduced to identify patients with axillary pCR to minimize the risk of morbidity.[7-9] However, the lack of long-term oncologic safety data and the overall false-negative rates of these less invasive staging procedures are a concern, and, therefore, ALND is still often performed in current clinical practice.[7,9-12] Identifying patients in whom axillary pCR is most likely can improve patient selection for less invasive staging procedures. In this systematic review and meta-analysis of patients with cN-positive disease treated with NST, the aim was to provide pooled data of axillary pCR rates for different breast cancer subtypes and their association with survival.

Key Points

Question What are the rates of axillary pathologic complete response (pCR) for different breast cancer subtypes in patients with initially clinically node-positive breast cancer?

Findings This systematic review and meta-analysis, including 33 unique studies with 57 531 unique patients, showed that the hormone receptor (HR)–negative/*ERBB2*-positive subtype was associated with the highest axillary pCR rate (60%). The remaining subtypes were associated with the following axillary pCR rates in decreasing order: 59% for *ERBB2*-positive, 48% for triple-negative, 45% for HR-positive/*ERBB2*-positive, 35% for luminal B, 18% for HR-positive/*ERBB2*-negative, and 13% for luminal A breast cancer.

Meaning These data can help estimate axillary treatment response in the neoadjuvant setting and thus select patients for more or less invasive axillary procedures.

Methods

Systematic Literature Search

For this systematic review and meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were applicable.[13] Embase and PubMed were searched on July 16, 2020, for studies assessing axillary pCR and/or survival outcomes for different breast cancer subtypes in patients with initially cN-positive disease. Details of both search strategies are provided in eMethods 1 and 2 in the Supplement.

Eligibility Criteria for Study Inclusion

Studies were eligible for inclusion if the axillary pCR rates were reported for 1 or more different subtypes in patients with cN-positive disease, including studies with and without pathologically proven axillary lymph node metastases at diagnosis before NST. Studies that assessed survival were eligible only if they included patients who had pathologically proven cN-positive disease. Female patients with breast cancer had to be treated with neoadjuvant chemotherapy, with or without *ERBB2* (formerly *HER2*)-targeted therapy, followed by any type of axillary surgery. Studies based on neoadjuvant endocrine or radiation therapy, with fewer than 10 patients per subtype, or with sentinel lymph node biopsy (SLNB) performed before NST, were excluded. Only randomized clinical trials, case-control studies, and cohort studies published in English were included.

Outcome Measures

The primary outcome of this study was the rate of axillary pCR and residual axillary lymph node disease after NST for different breast cancer subtypes, differentiating studies with and without patients with pathologically proven cN-positive disease. The secondary outcome of this study was survival divided by axillary pCR and residual axillary lymph node disease for different subtypes.

Study Selection

The title and abstract of all studies were independently screened by 2 reviewers (S.S. and J.M.S.). Afterward, the full text of each remaining study was read and assessed for eligibility. In addition, the reference lists of the included studies were manually checked to identify further eligible studies.

Data Extraction and Analysis

The following study characteristics were extracted from the included studies by the 2 reviewers independently: first author, year of publication, country, study design, evaluable sample size, clinical tumor and nodal stage, definition of subtypes, NST regimens, type of axillary surgery, and definition of axillary pCR. Discrepancies of data extraction were resolved during a consensus meeting. The extracted data were divided by studies with and without patients with pathologically proven cN-positive disease. The first group included only studies in which the whole study population had cytologically or pathologically proven axillary lymph node metastases. In studies without patients with pathologically proven cN-positive disease, nodal positivity was based on physical examination and imaging findings, or only part of the study population had pathologically proven axillary lymph node metastases. The statistical analyses were performed in Stata/SE, version 16.0 (StataCorp LLC). The random-effects model for meta-analysis in the metaprop command of Stata/SE was used to calculate the overall pooled estimate of axillary pCR for each subtype, regardless of the type of axillary surgery.[14] A subanalysis was performed for studies with the reference standard ALND and for axillary pCR definition. The computed variation of axillary pCR effect size estimates with 95% CI and weights for each subtype was visualized in forest plots divided into studies of patients with and without (or not always) pathologically proven cN-positive disease. The variability of axillary pCR estimates due to heterogeneity among

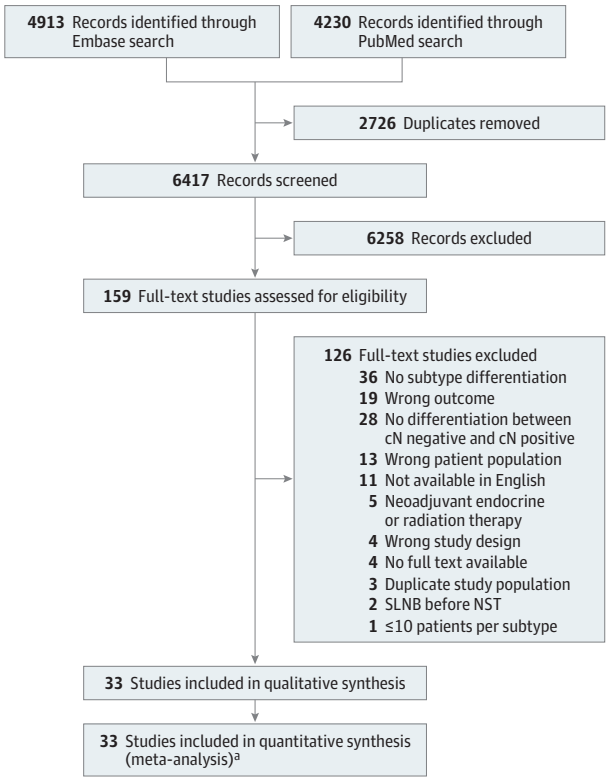
the included studies was quantified using the I^2 index.[15] The χ^2 test was used to assess statistical heterogeneity. Two-sided $P < .05$ was considered statistically significant.

Results

Systematic Literature Search and Study Selection

A total of 9143 records were identified from the systematic literature, of which 2726 duplicate records were removed. After title and abstract screening of the remaining records, 159 studies were selected for full-text review. Eventually, 33 studies[6,16-47] were included for qualitative and quantitative analysis after full-text assessment. The flow diagram of study selection is shown in **Figure 1**. Assessment of the reference lists did not yield further eligible articles. All 33 included studies reported on axillary pCR rates for different subtypes, and 1 of the 33 studies[16] reported on survival outcome of axillary pCR and residual axillary lymph node disease for different subtypes.

Figure 1. PRISMA Flow Diagram for Study Selection



NST indicates neoadjuvant systemic therapy; SLNB, sentinel lymph node biopsy.

[a] Includes 33 studies on axillary pCR rates, of which 1 study also reported on the second study aim of survival outcome.

Study Characteristics

A total of 57 531 patients were included. In 23 studies (9961 patients),[6,16,17,19-38] all the patients had pathologically proven axillary lymph node metastases before NST. In the remaining 10 studies (47 570 patients),[18,39-47] nodal positivity was solely based on results of the physical examination and imaging, or only part of the study population had pathologically proven axillary lymph node metastases before NST. The **Table** depicts the general characteristics of all included studies. Most studies (20 of 33) included cT1 to cT4 disease. Axillary pCR was defined as ypN0 in 15 studies,[19,21,23,25,26,30-32,34,38,39,41,43,44,47] as ypN0 with isolated tumor cells (itc) in 15 studies,[6,16,18,22,24,28,29,33,35-37,40,42,45,46] as ypN0/itc with micrometastases (mi) in 1 study,[20] and not reported in 2 studies.[17,27] Axillary lymph node dissection was routinely performed in all patients in 18 of the 33 studies.[6,16,19,20,22,25,26,28-31,33,35,36,38,40,41,43] In the other studies, either SLNB or targeted axillary dissection (TAD) with or without ALND was performed. In total, 7 different subtypes were identified, and each patient was included only in 1 subtype: hormone receptor (HR)-positive/*ERBB2*-positive, HR-positive/*ERBB2*-negative, HR-negative/*ERBB2*-positive, triple-negative, *ERBB2*-positive (unknown whether HR-positive or HR-negative), luminal A (HR-positive, *ERBB2*-negative, low levels of Ki-67), luminal B/*ERBB2*-negative (HR-positive, *ERBB2*-negative, high levels of Ki-67), and luminal B/*ERBB2*-positive (HR-positive, *ERBB2*-positive, any Ki-67 level).

HR-Positive/*ERBB2*-Positive Breast Cancer

Seventeen studies[6,17-20,24,25,27-29,31,33,35,36,38,41,47] including 8168 patients reported on HR-positive/*ERBB2*-positive breast cancer: 1225 with pathologically proven and 6943 without (or not always) pathologically proven cN-positive disease (**Figure 2**A). In 12 studies (3730 patients),[6,19,20,25,28,29,31,33,35,36,38,41] the reference standard was ALND, and in 5 studies (4438 patients),[17,18,24,27,47] it was SLNB or ALND. Axillary pCR was defined as ypN0/itc/mi in 1 study (26 patients),[20] ypN0/itc in 8 studies (3612 patients),[6,18,24,28,29,33,35,36] ypN0 in 6 studies (4325 patients),[19,25,31,38,41,47] and not reported in 2 studies (205 patients).[17,27] The overall pooled axillary pCR rate was 45% (95% CI, 40%-51%) (45% [95% CI, 37%-53%] for patients with pathologically proven and 47% [95% CI, 38%-57%] for those without [or not always] pathologically proven cN-positive disease) (eTable in the Supplement). Between the studies, significant heterogeneity was seen with an I^2 index of 93.31% ($P < .001$). The pooled axillary pCR rate was 42% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 48% for ypN0/itc and 40% for ypN0.

HR-Positive/*ERBB2*-Negative Breast Cancer

Twenty-five studies[17-22,24-36,38,40,42,44,46,47] including 26 322 patients reported on HR-positive/*ERBB2*-negative breast cancer: 4340 with pathologically proven and 21 982 without (or not always) pathologically proven cN-positive disease (Figure 2B). In 14 studies (11 921 patients),[19,20,22,25,26,28-30,33,35-41] the reference standard was ALND; in 8 studies (14 036 patients),[17,18,21,24,27,42,46,47] SLNB or ALND; in 1 study (27 patients),[34] TAD or ALND; in 1 study (41 patients),[32] SLNB; and in 1 study (297 patients),[44] was not reported. Axillary pCR was defined as ypN0/itc/mi in 1 study (30 patients),[20]

Table. General Characteristics of Included Studies in Qualitative and Quantitative Analysis, Divided by Studies of Patients With and Without Pathologically Proven Clinically Node-Positive Disease

Source	Country	Center	Study type	No. of participants	cT category	cN category	Cancer subtype	NST	Axillary surgery	Definition of axillary pCR
Studies of patients with pathologically proven clinically node-positive disease										
Al-Hatalli et al,[20] 2019	UK	Single	Retrospective	87	1-4	1-3	HR positive/*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab	ALND	ypN0/itc/mi
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Bi et al,[21] 2019	China	Single	Retrospective	495	1-4	1-3	*ERBB2* positive	Anthracycline and taxane with or without trastuzumab	SLNB, ALND	ypN0
							HR positive/*ERBB2* negative			
							TN			
Boughey et al,[22] 2017	US	Multiple	Prospective	701	0-3	1-2	*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab; no anthracycline and no taxane	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							TN			
Cerbelli et al,[23] 2019	Italy	Single	Retrospective	181	1-4	1-3	Luminal A	Anthracycline, cyclophosphamide, and taxane with or without trastuzumab	SLNB, ALND	ypN0
							Luminal B/*ERBB2* negative			
							Luminal B/*ERBB2* positive			
							HR negative/*ERBB2* positive			
							TN			
Choi et al,[24] 2019	Korea	Single	Retrospective	844	1-3	1-3	HR positive/*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab	SLNB, ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Dominici et al,[6] 2010	US	Single	Prospective	109	0-4	1-3	HR positive/*ERBB2* positive	Anthracycline or taxane with or without trastuzumab	ALND	ypN0/itc
							HR negative/*ERBB2* positive			
Enokido et al,[25] 2016	Japan	Multiple	Prospective	130	1-3	1	HR positive/*ERBB2* positive	NR	ALND	ypN0
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Fernandez-Gonzalez et al,[16] 2020	Spain	Single	Retrospective	330	0-4	1-2	Luminal A	Anthracycline and taxane with or without trastuzumab	ALND	ypN0/itc
							Luminal B/*ERBB2* negative			
							Luminal B/*ERBB2* positive			
							HR negative/*ERBB2* positive			
							TN			
Glaeser et al,[26] 2019	Germany	Single	Retrospective	72	1-4	1-3	*ERBB2* positive	Taxane with or without trastuzumab	ALND	ypN0
							HR positive/*ERBB2* negative			
							TN			
Ha et al,[27] 2018	US	Single	Retrospective	127	NR	NR	HR positive/*ERBB2* positive	Anthracycline and taxane	SLNB, ALND	NR
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			

(continued)

Table. General Characteristics of Included Studies in Qualitative and Quantitative Analysis, Divided by Studies of Patients With and Without Pathologically Proven Clinically Node-Positive Disease (continued)

Source	Country	Center	Study type	No. of participants	cT category	cN category	Cancer subtype	NST	Axillary surgery	Definition of axillary pCR
Kim et al,[28] 2019	Korea	Single	Retrospective	244	1-4	1-3	HR positive/*ERBB2* positive	Anthracycline and taxane with or without trastuzumab	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Kim et al,[29] 2015	Korea	Single	Retrospective	415	1-4	1-3	HR positive/*ERBB2* positive	Anthracycline and/or taxane; no anthracycline and no taxane	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Koolen et al,[30] 2013	The Netherlands	Single	Prospective	80	1-4	1-3	*ERBB2* positive	Taxane, platinum, and trastuzumab; anthracycline and cyclophosphamide	ALND	ypN0
							HR positive/*ERBB2* negative			
							TN			
Li et al,[31] 2014	China	Single	Retrospective	157	1-4	1-3	HR positive/*ERBB2* positive	Taxane, platinum, and trastuzumab	ALND	ypN0
							HR negative/*ERBB2* positive			
Mougalian et al,[17] 2016	US	Single	Retrospective	1346	0-4	1-3	HR positive/*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab	SLNB, ALND	NR
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Park et al,[32] 2017	Korea	Single	Retrospective	86	1-4[a]	1-3	*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab	SLNB	ypN0
							HR positive/*ERBB2* negative			
							TN			
Park et al,[33] 2013	Korea	Single	Retrospective	169	1-3	NR	HR positive/*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Qu et al,[34] 2018	US	Single	Retrospective	59	NR	NR	*ERBB2* positive	NR	TAD, ALND	ypN0
							HR positive/*ERBB2* negative			
							TN			
Samiei et al,[35] 2019	The Netherlands	Multiple	Retrospective	2410	1-3	1	HR positive/*ERBB2* positive	Anthracycline, cyclophosphamide, with or without taxane or fluorouracil	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Schipper et al,[36] 2014	The Netherlands	Multiple	Retrospective	291	1-4	NR	HR positive/*ERBB2* positive	Anthracycline and cyclophosphamide with or without taxane	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Tadros et al,[37] 2017	US	Single	Retrospective	237	1-2	1	*ERBB2* positive	Anthracycline and/or taxane with or without trastuzumab with or without pertuzumab	NR	ypN0/itc
							TN			

(continued)

Table. General Characteristics of Included Studies in Qualitative and Quantitative Analysis, Divided by Studies of Patients With and Without Pathologically Proven Clinically Node-Positive Disease (continued)

Source	Country	Center	Study type	No. of participants	cT category	cN category	Cancer subtype	NST	Axillary surgery	Definition of axillary pCR
van Nijnatten et al,[19] 2017	The Netherlands	Multiple	Retrospective	1258	0-4[a]	NR	HR positive/*ERBB2* positive	Anthracycline, cyclophosphamide, and taxane or fluorouracil with or without trastuzumab	ALND	ypN0
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Wu et al,[38] 2019	China	Single	Prospective	133	0-3	1-3	HR positive/*ERBB2* positive	Taxane with or without anthracycline or platinum with or without trastuzumab with or without pertuzumab	ALND	ypN0
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Studies of patients without pathologically proven clinically node-positive disease (or only part of the study population)										
DiMicco et al,[39] 2019	Italy	Single	Retrospective	176	1-4	NR	Luminal A	Anthracycline and taxane	SLNB, ALND	ypN0
							Luminal B			
							HR negative/*ERBB2* positive			
							TN			
Fayanju et al,[18] 2018	US	Multiple	Retrospective	15 078	1-3	1	HR positive/*ERBB2* positive	NR	SLNB, ALND[b]	ypN0/itc
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Gentile et al,[40] 2017	US	Single	Retrospective	310	1-4	1-3	*ERBB2* positive	Anthracycline, cyclophosphamide with or without taxane; cyclophosphamide, methotrexate, and fluorouracil; cyclophosphamide, taxane, with or without vinorelbine; taxane only; platinum only; anthracycline and taxane	ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							TN			
Kantor et al,[41] 2018	US	Multiple	Retrospective	18 052	1-4[a]	1-3	HR positive/*ERBB2* positive	NR	ALND	ypN0
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			
Lee et al,[42] 2019	US	Single	Retrospective	195	1-4	1-3	*ERBB2* positive	NR	SLNB, ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							TN			
Ouldamer et al,[43] 2018	France	Single	Retrospective	116	2-4	1	Luminal A	NR	ALND	ypN0
							Luminal B			
							HR negative/*ERBB2* positive			
							TN			
Petruolo et al,[44] 2017	US	Single	Retrospective	297	1-4[a]	1-3	HR positive/*ERBB2* negative	Anthracycline, cyclophosphamide, and taxane	NR	ypN0

(continued)

ypN0/itc in 11 studies (9326 patients),[18,22,24,28,29,33,35,36,40,42,46] ypN0 in 11 studies (16 188 patients),[19,21,25,26,30,32,34,38,41,44,47] and not reported in 2 studies (778 patients).[17,27] The pooled axillary pCR rate was 18% (95% CI, 14%-21%) (17% [95% CI, 13%-25%] for pathologically proven and 18% [95% CI, 13%-25%] for not [or not always] pathologically proven cN-positive disease)

Table. General Characteristics of Included Studies in Qualitative and Quantitative Analysis, Divided by Studies of Patients With and Without Pathologically Proven Clinically Node-Positive Disease (continued)

Source	Country	Center	Study type	No. of participants	cT category	cN category	Cancer subtype	NST	Axillary surgery	Definition of axillary pCR
Resende et al,[45] 2018	Brazil	Single	Retrospective	228	1-4	1-3	Luminal A	Anthracycline, cyclophosphamide, and taxane with or without platinum	NR	ypN0/itc
							Luminal B			
							HR negative/*ERBB2* positive			
							TN			
Steiman et al,[46] 2016	US	Single	Retrospective	135	NR	1-3	*ERBB2* positive	NR	SLNB, ALND	ypN0/itc
							HR positive/*ERBB2* negative			
							TN			
Wong et al,[47] 2019	US	Multiple	Retrospective	12 983	1-3	1-2	HR positive/*ERBB2* positive	NR	SLNB, ALND	ypN0
							HR positive/*ERBB2* negative			
							HR negative/*ERBB2* positive			
							TN			

Abbreviations: ALND, axillary lymph node dissection; HR, hormone receptor; itc, isolated tumor cells; mi, micrometastases; NR, not reported; 5 NST, neoadjuvant systemic therapy; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TN, triple negative.

[a] Clinical tumor stage was not available in a small number of patients.

[b] Axillary surgery was defined by the number of lymph nodes removed.

(eTable in the Supplement). Between the studies, significant heterogeneity was seen with an I^2 index of 97.18% ($P < .001$). The pooled axillary pCR rate was 16% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 20% for ypN0/itc and 15% for ypN0.

HR-Negative/*ERBB2*-Positive Breast Cancer

Twenty-three studies[6,16-20,23-25,27-31,33,35,36,38,39,41,43,45,47] including 7132 patients reported on HR-negative/*ERBB2*-positive breast cancer: 1357 with pathologically proven and 5775 without (or not always) pathologically proven cN-positive disease (**Figure 3**A). In 15 studies (3034 patients),[6,16,20,25,28-31,33,35-38,41,43] the reference standard was ALND; in 7 studies (4041 patients),[17,18,23,24,27,39,47] SLNB or ALND; and in 1 study (57 patients),[45] not reported. Axillary pCR was defined as ypN0/itc/mi in 1 study (8 patients),[20] ypN0/itc in 10 studies (2440 patients),[6,16,18,24,25,28,29,33,35,36] ypN0 in 10 studies (4516 patients),[19,21,25,30,31,38,39,41,43,47] and not reported in 2 studies (168 patients).[17,27] The pooled axillary pCR was 60% (95% CI, 55%-65%) (60% [95% CI, 53%-68%] for patients with and 60% [95% CI, 51%-69%] for those without [or not always] pathologically proven cN-positive disease) (eTable in the Supplement). Between the studies, significant heterogeneity was seen with an I^2 index of 91.96% ($P < .001$). The pooled axillary pCR rate was 57% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 56% for ypN0/itc and 64% for ypN0.

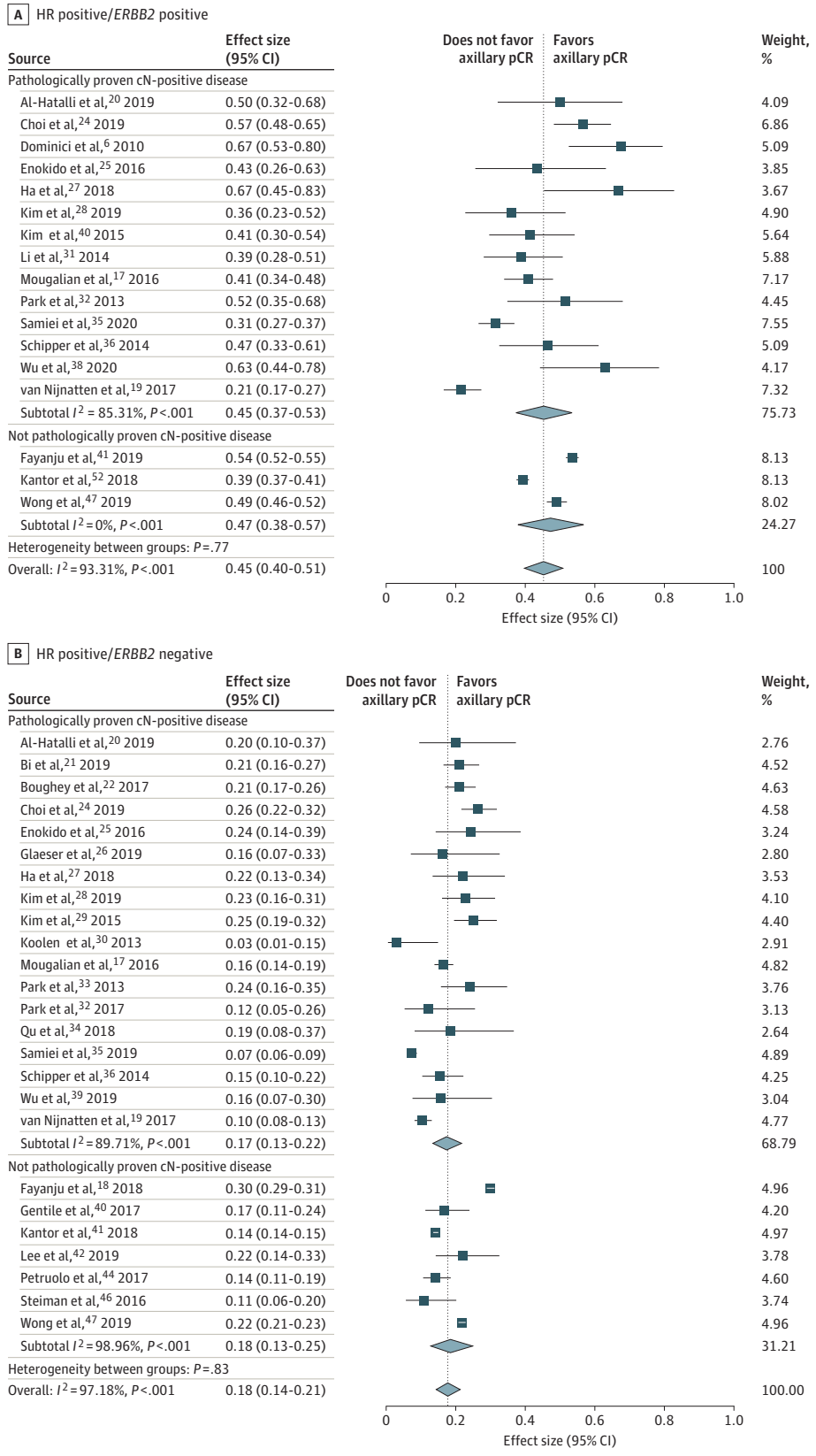
Triple-Negative Breast Cancer

Thirty studies[16-30,32-43,45-47] including 14 521 patients reported on triple-negative breast cancer: 2164 with pathologically proven and 12 357 without (or not always) pathologically proven cN-positive disease (Figure 3B). In 16 studies (5759 patients),[16,19,20,22,25,26,28-30,33,35,36,38,40,41,43] the reference standard was ALND; in 10 studies (8548 patients),[17,18,21,23,24,27,39,42,46,47] SLNB or ALND; in 1 study (14 patients),[34] TAD or ALND; in 1 study (29 patients),[32] SLNB; and in 2 studies (171 patients),[37,45] not reported. Axillary pCR was defined as ypN0/itc/mi in 1 study (23 patients),[20] ypN0/itc in 14 studies (5449 patients),[16,18,22,24,28,29,33,35-37,40,42,45,46] ypN0 in 13 studies (8727 patients),[19,21,23,25,26,30,32,34,38,39,41,43,47] and not reported in 2 studies (322 patients).[17,27] The pooled axillary pCR rate was 48% (95% CI, 44%-53%) (48% [95% CI, 42%-54%] for pathologically proven and 50% [95% CI, 41%-58%] for not [or not always] pathologically proven cN-positive disease) (eTable in the Supplement). Between the studies, significant heterogeneity was seen with an I^2 index of 95.15% ($P < .001$). The pooled axillary pCR rate was 47% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 47% for ypN0/itc and 52% for ypN0.

Luminal A Breast Cancer

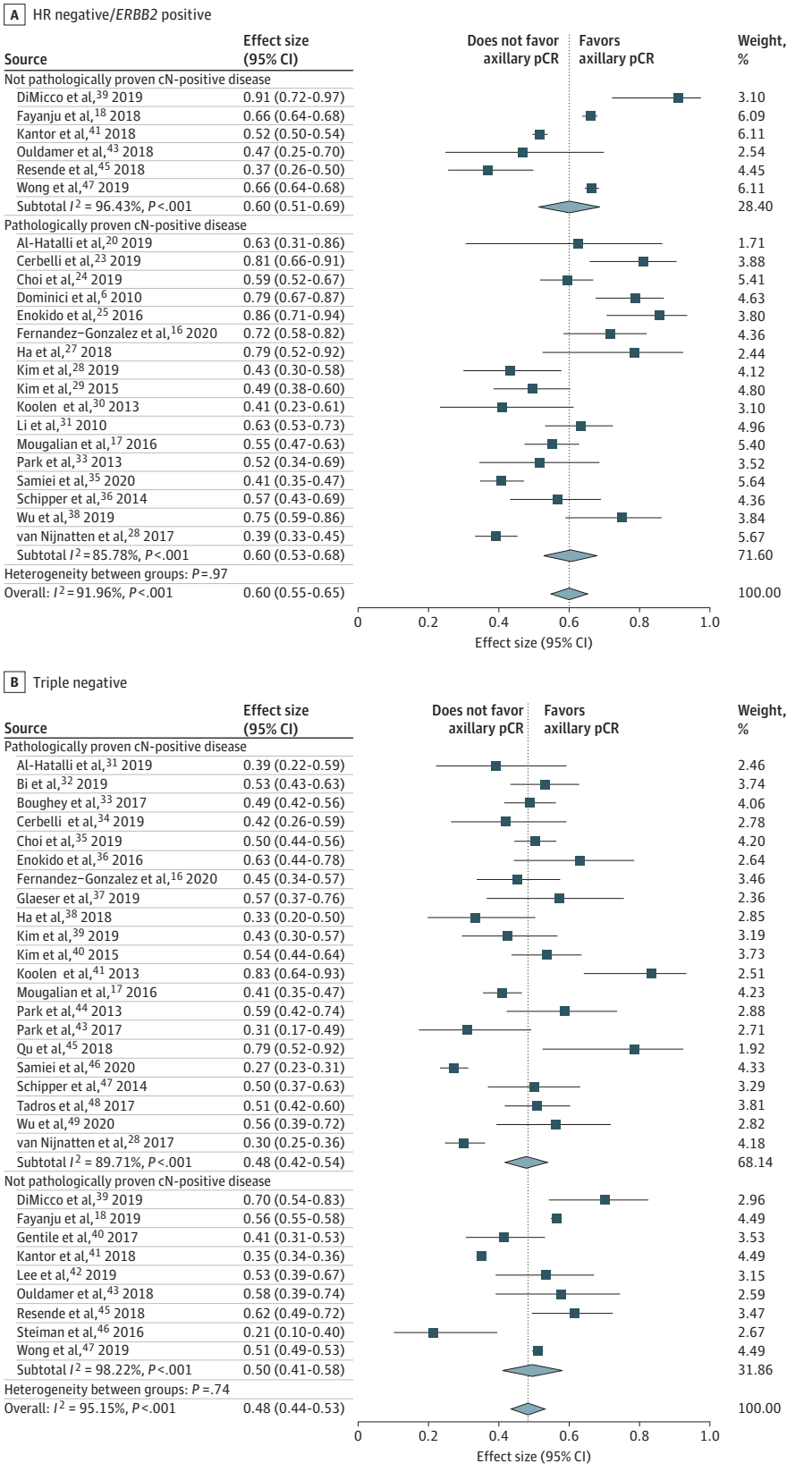
Five studies[16,23,39,43,45] including 156 patients reported on luminal A breast cancer: 54 with pathologically proven and 102 without (or not always) pathologically proven cN-positive disease (**Figure 4**A). In 2 studies (77 patients),[16,43] the reference standard was ALND; in 2 studies (38 patients),[23,39] SLNB or ALND; and in 1 study (41 patients),[45] not reported. Axillary pCR was defined as ypN0/itc in 2 studies (77 patients)[16,45] and ypN0 in 3 studies (79 patients).[23,39,43] The pooled axillary pCR rate was 13% (95% CI, 5%-23%) (5% [95% CI, 0%-13%] for pathologically proven and 19% [95% CI, 12%-28%] for not [or not always] pathologically proven cN-positive disease) (eTable in the Supplement). Between the studies, heterogeneity was seen with an I^2 index of 58.70% ($P = .05$). The pooled axillary pCR rate was 13% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 8% for ypN0/itc and 20% for ypN0.

Figure 2. Forest Plots of Axillary Pathologic Complete Response (pCR) for Hormone Receptor (HR)–Positive/*ERBB2*-Positive and HR-Positive/*ERBB2*-Negative Breast Cancer Subtypes



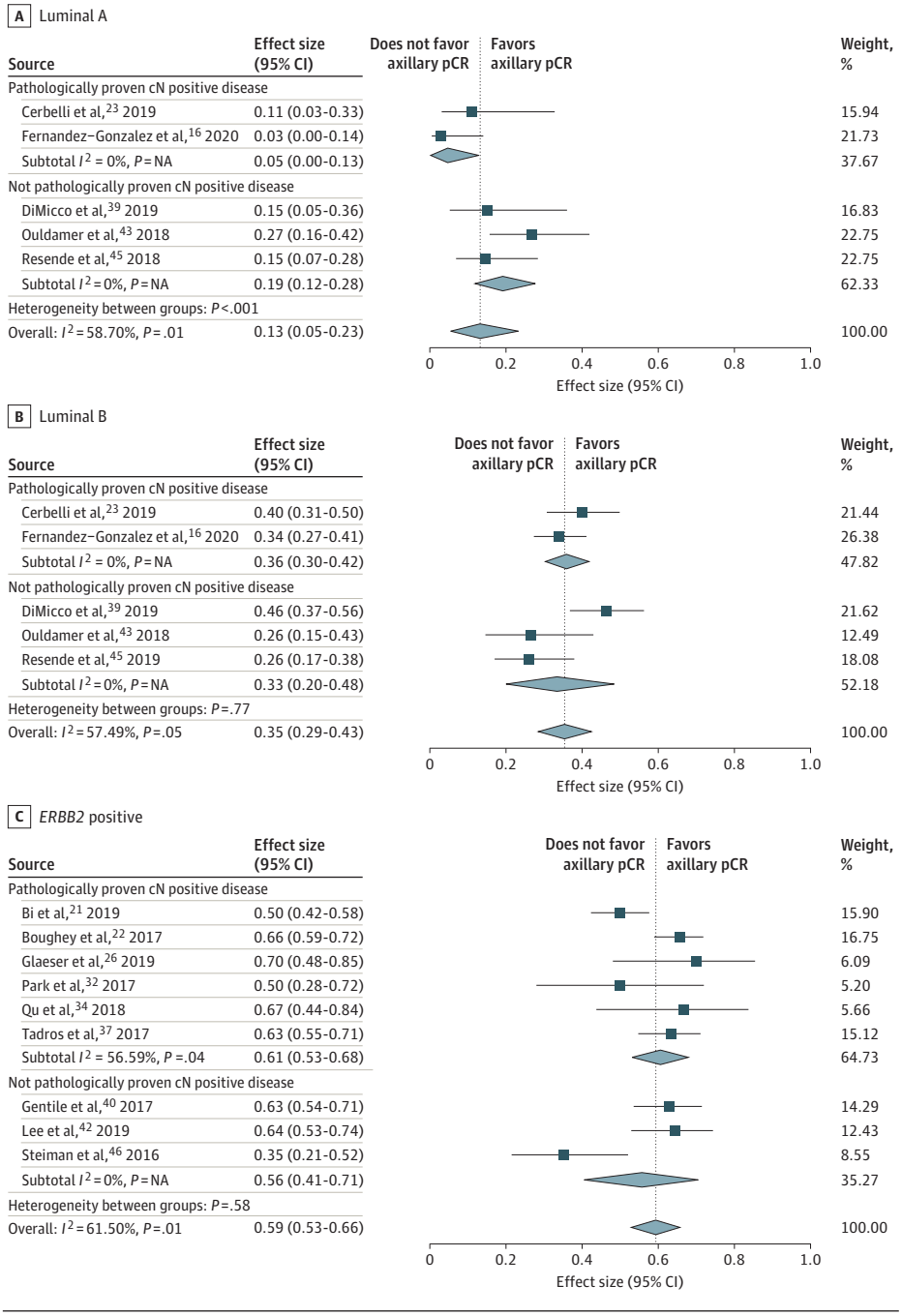
HR indicates hormone receptor. Diamonds indicate effect size.

Figure 3. Forest Plots of Axillary Pathologic Complete Response (pCR) for Hormone Receptor–Negative/*ERBB2*-Positive and Triple-Negative Breast Cancer Subtypes



HR indicates hormone receptor. Diamonds indicate effect size.

Figure 4. Forest Plots of Axillary Pathologic Complete Response (pCR) for 3 Breast Cancer Subtypes



Diamonds indicate effect sizes. NA indicates not applicable.

Luminal B Breast Cancer

Five studies[16,23,39,43,45] including 468 patients reported on luminal B breast cancer: 272 with pathologically proven and 196 without (or not always) pathologically proven cN-positive disease (Figure 4B). In 2 studies (211 patients),[16,43] the reference standard was ALND; in 2 studies (192 patients),[23,39] SLNB or ALND; and in 1 study (65 patients),[45] not reported. Axillary pCR was defined as ypN0/itc in 2 studies (242 patients)[16,45] and ypN0 in 3 studies (226 patients).[23,39,43] The pooled axillary pCR rate was 35% (95% CI, 29%-43%) (36% [95% CI, 30%-42%] for pathologically proven and 33% [95% CI, 20%-48%] for not [or not always] pathologically proven cN-positive disease) (eTable in the Supplement). Between the studies, heterogeneity was seen with an I^2 index of 57.49% (P = .05). The pooled axillary pCR rate was 33% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 32% for ypN0/itc and 39% for ypN0.

ERBB2-Positive Breast Cancer

Nine studies[21,22,26,32,34,37,40,42,46] including 764 patients reported on *ERBB2*-positive breast cancer: 549 with pathologi-

cally proven and 215 without (or not always) pathologically proven cN-positive disease (Figure 4C). In 3 studies (332 patients),[22,26,40] the reference standard was ALND; in 3 studies (267 patients),[21,42,46] SLNB or ALND; in 1 study (18 patients),[34] TAD or ALND; in 1 study (16 patients),[32] SLNB; and in 1 study (131 patients),[37] not reported. Axillary pCR was defined as ypN0/itc in 5 studies (550 patients)[22,37,40,42,46] and ypN0 in 4 studies (214 patients).[21,26,32,34] The pooled axillary pCR rate was 59% (95% CI, 53%-66%) (61% [95% CI, 53%-68%] for pathologically proven and 56% [95% CI, 41%-71%] for not [or not always] pathologically proven cN-positive disease) (eTable in the Supplement). Between the studies, significant heterogeneity was seen with an I^2 index of 61.50% (P = .01). The pooled axillary pCR rate was 65% for studies with the reference standard ALND. Regarding pCR definition, the pooled axillary pCR rate was 61% for ypN0/itc and 56% for ypN0.

Survival by Axillary Treatment Response and Subtype

Fernandez-Gonzalez et al[16] evaluated 330 patients with pathologically proven cN-positive disease treated with NST and subsequent ALND: 36 with luminal A, 115 with luminal B (*ERBB2*-negative), 62 with luminal B (*ERBB2*-positive), 53 with HR-negative/*ERBB2*-positive, and 64 with triple-negative breast cancer. For all subtypes, distant disease-free survival (defined as the time from the initiation of NST until distant recurrence, second primary cancer, or death due to any cause) and overall survival were improved for patients with axillary pCR compared with those with residual axillary lymph node disease. The differences in distant disease-free survival and overall survival between subtypes were minimal in patients who achieved axillary pCR.

Discussion

This is the first systematic review and meta-analysis, to our knowledge, to investigate axillary pCR rates for different breast cancer subtypes, for patients both with and without (or not always) pathologically proven clinically node-positive disease. All 7 subtypes reported in the included articles were incorporated into the analysis to increase the clinical utility of the results. The pooled analysis of 57 531 patients showed that the HR-negative/*ERBB2*-positive subtype was associated with the highest axillary pCR rate (60%). In decreasing order, the remaining subtypes were associated with the following axillary pCR rates: 59% for *ERBB2*-positive, 48% for triple-negative, 45% for HR-positive/*ERBB2*-positive, 35% for luminal B, 18% for HR-positive/*ERBB2*-negative, and 13% for luminal A breast cancer. In general, no major differences were found in the axillary pCR rates by analyzing separately the studies including patients with and without pathologically proven cN-positive disease.

Houssami et al[3] performed a meta-analysis on this association and found that the triple-negative and HR-negative/*ERBB2*-positive subtypes have the highest chance of achieving a pCR. Contrary to the meta-analysis of Houssami et al,[3] the current meta-analysis only included patients with cN-positive disease and specifically focused on axillary pCR rather than overall or breast-only pCR. Equal to the meta-analysis by Houssami et al,[3] the triple-negative and HR-negative/*ERBB2*-positive subtypes were associated with the highest pCR rates. In addition to the association between treatment response and subtype, multiple studies have reported on the strong positive correlation between pCR and survival. In a pooled analysis of 12 studies of patients with breast cancer treated in the neoadjuvant setting, Cortazar et al[1] reported that a pCR of both the breast and axilla was associated with improved survival compared with a pCR of the breast, irrespective of axillary treatment response. This correlation was especially strong in the triple-negative and HR-negative/*ERBB2*-positive (treated with *ERBB2*-targeted therapy) subtypes. Furthermore, a few studies have reported the effect on survival in patients with cN-positive breast cancer who achieved an axillary pCR. In these patients, it seems that achieving a pCR of the axilla has a greater effect on survival than achieving a breast pCR. In a study of 1600 patients with cN-positive disease, Mougalian et al[17] found that patients with an axillary pCR but residual breast disease have improved survival compared with patients with a breast pCR but residual axillary disease. Fayanju et al[18] reported that the prognostic impact of breast-only pCR or axilla-only pCR depends on subtype. In the current meta-analysis, only 1 study[16] included reported on survival for different subtypes stratified by axillary treatment response. This study suggested that in the case of axillary pCR, survival is no longer substantially different among subtypes. Further research is needed to determine whether the correlation between axillary pCR and survival may vary among different subtypes.

To avoid overtreatment of the axilla in patients with cN-positive disease who achieve an axillary pCR, several less invasive staging procedures have been proposed to replace ALND. Among these are SLNB,[48-50] the removal of the pretreatment positive lymph node (for example, the MARI [marking axillary lymph node with radioactive iodine seeds] procedure),[9] and TAD[7] (excision of both the pretreatment marked positive lymph node and the SLN[s]). In a meta-analysis on the diagnostic accuracy of these different staging procedures,[51] TAD appeared to be most accurate. However, strong evidence to confirm this is lacking. Moreover, whether the accuracy of less invasive staging procedures depends on subtype remains unknown. In the current meta-analysis, pooled axillary pCR rates were generally lower for studies in which all patients had undergone ALND. This can be explained by the superior diagnostic accuracy of ALND and, consequently, increased detection of residual axillary disease. Whether the diminished accuracy of these less invasive staging procedures compared with ALND impairs long-term survival remains unknown. Despite the lack of evidence on long-term outcomes of patients with cN-positive disease in whom ALND is omitted after NST, ALND is already increasingly being replaced by less invasive staging procedures.[52-54] This trend is occurring in all subtypes. Therefore, data on long-term outcomes are urgently needed to further advance response-based treatment while considering tumor biology.

The results of this systematic review and meta-analysis may have implications not only for patients with axillary pCR but also for patients with residual axillary disease. Two recent trials reported on the benefit of treatment with additional adjuvant systemic therapy in patients with residual disease after NST. In the KATHERINE trial,[55] patients with *ERBB2*-positive cancer and residual disease were treated with adjuvant trastuzumab emtansine, and in the CREATE-X trial,[56] patients with *ERBB2*-negative cancer and residual disease were treated with adjuvant capecitabine. Both trials reported improved disease-free survival. These trials demonstrated that adequate assessment of treatment response is pivotal. The data of the current review can help estimate axillary treatment response and thus improve patient selection for appropriate axillary staging and adjuvant treatment.

Limitations

This review is limited by the heterogeneity of the included studies. To account for the different definitions of cN-positive disease and pCR, and for the extent of axillary surgery, subanalyses were performed. We expected that studies with pathologically proven cN-positive disease would show a lower overall axillary pCR rate. However, the differences found in this meta-analysis were not substantial, except for luminal A breast cancer, which could have been caused by the small number of patients and/or tumor heterogeneity. The small differences in the other subtypes can be explained by the fact that a part of the study population had pathologically proven cN-positive disease. Conflicting results have been published regarding the prognosis of ypN0 and residual isolated tumor cells and/or micrometastases.[19,57,58] In the present study, both decreased and increased axillary pCR rates were observed depending on subtype when ypN0 was compared with ypN0/itc. Further research is needed to determine the optimal definition of axillary pCR and whether limited residual nodal disease should be regarded as a separate entity. Apart from this, most studies classified subtypes based on traditional markers, and data were limited for molecularly classified subtypes (including Ki-67 status).

Conclusions

Axillary pCR rates in patients with initially cN-positive breast cancer who are treated with NST strongly depend on subtype. The HR-negative/*ERBB2*-positive subtype had the highest pooled axillary pCR rate. Whether the correlation between axillary pCR and survival is stronger in certain subtypes is still unknown. Data on long-term outcomes stratified by subtype, axillary treatment response, and the extent of surgery are urgently needed, especially in an era when ALND is increasingly being replaced by less invasive staging procedures.

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